REMARKS

Applicants cited at page 17, lines 15-17 of the reply filed March 6, 2008 the following reference: *Book of Abstracts*, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000. A hard copy of which was not included with the March 6, 2008 reply. Applicants here include a copy of the aforementioned reference as **Exhibit 11**.

Applicants respectfully submit that this application is in condition for allowance. An early reconsideration and Notice of Allowance are respectfully requested.

Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark Konieczny, Reg. No. 47,715 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: MAR 13 2008

Respectfully submitted,

By _____
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

JMK

Attachments: Exhibit 11

ABSTRACTS OF PAPERS

Part 2

219th ACS National Meeting
0-8412-3731-X

American Chemical Society

San Francisco, CA

March 26-30, 2000

506.

STERIC AND ELECTRONIC CONTRIBUTIONS TO SUBSTITUENT EFFECTS ON CARBON AND HYDROGEN CHEMICAL SHIFTS. *Peter Rudolf Seidl, Escola de Química, UFRJ, Cidade Universitária, Rio de Janeiro, Brazil, pseidl@uol.com.br, Kátia Zaccur Leal, Departamento de Físico-Química, UFF, Outeiro de São João Batista, s/n, Niterói, 24020-150, Brazil, Valentim Emílio Uberti Costa, Departamento de Química Orgânica, UFRGS, Porto Alegre, 91509-900, Brazil, José Glauco Ribeiro Tostes, Centro de Ciências e Tecnologia, UENF, Campos, 28015-620, Brazil, José Walkimar de Mesquita Carneiro, Departamento de Química Geral e Inorgânica, UFF, Outeiro de São João Batista, s/n, Niterói, 24020-150, Brazil, and Jacques Fernandes Dias, Departamento de Química, IME, Praça General Tibúrcio, 80 - Praia Vermelha, 22290-270, Brazil.*

Methods for calculating physical and chemical properties of molecules in general and chemical shift tensors in particular have made extraordinary progress in recent years. It is thus now possible to take a closer look at the phenomena that contribute to chemical shifts. "Substituent effects" play an very important role in this respect and ever since some of the earliest work on hydrogen and carbon chemical shifts, this approach has contributed enormously to their understanding. Norbornyl and adamantyl systems, two of those most commonly studied in this respect, were used as models for the present work. ubstituent effects of alkyl groups were compared to those of oxygen (princi- pally of a hydroxyl group) so as to separate steric and electronic contributions to chemical shifts. Supplementary calculations of structures were made by B3LYP/6-31G(d) methods while shielding calculations were made by DFT-GIAO methods at the B3LYP level with 6-31G(d) basis sets. Steric effects can be traced to bond polarization contributions or angular deformation while electronic contributions are mostly due to hyperconjugation or the proximity of the hydroxyl hydrogen.

507.

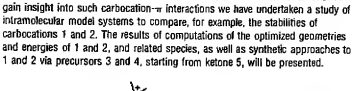
THEORETICAL CRITICAL DISTANCE MODEL FOR THE ENERGY OF ACTIVATION IN THE BERGMAN CYCLIZATION OF ENEDIYNES. *Joseph F. Capitani and Abhijit Mitra, Graduate Program in Biotechnology and Department of Chemistry & Biochemistry, Manhattan College/College of Mount St. Vincent, Riverdale, NY 10471, fax: 718-862-7814, jcapitan@manhattan.edu*

Molecules containing the 3-ene-1,5-diyne functionality have recently been shown to be potent anticancer agents. These molecules undergo a Bergman cyclization that leads to the formation of a 1,4-diradical which then cleaves a DNA molecule by hydrogen abstraction from the C-5 position of the nucleoside. A theoretical model to predict the ease of cyclization of a class of enediyne molecules has ⁿen developed. This model involves the expansion of the reaction profile as a ₋ubic polynomial, with the expansion coefficients supplied by density functional theory at the B3LYP/cc-pVTZ level calculations, to construct a calibration curve. The use of other electronic parameters to predict rate data is discussed.

508.

BENZOBICYCLO[4.2.1]NONENE MODEL SYSTEM FOR STUDY OF CARBOCATION-π INTERACTION. *Janeta V. Popovici-Müller, Robert Ditchfield, and Thomas A. Spencer Jr. Department of Chemistry, Dartmouth College, 6128 Burke Laboratory, Hanover, NH 03755, fax: 603-646-3946, Janeta.V.Popovici-Muller@Dartmouth.EDU*

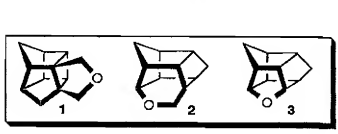
Interaction with aromatic π systems has become recognized as an important mode of stabilization of carbocation intermediates in biochemical reactions. To gain insight into such carbocation-π interactions we have undertaken a study of intramolecular model systems to compare, for example, the stabilities of carbocations 1 and 2. The results of computations of the optimized geometries and energies of 1 and 2, and related species, as well as synthetic approaches to 1 and 2 via precursors 3 and 4, starting from ketone 5, will be presented.



509.

SYNTHESIS OF NOVEL, CAGE-ANNULATED OXAHETEROCYCLES. *Alan P. Marchand, Irishi N. N. Namboothiri, and Satish Kumar Vadlakonda. Department of Chemistry, University of North Texas, NT Station, Box 305070, Denton, TX 76203, fax: 940-369-7374*

Procedures used to synthesize three novel, cage-annulated oxaheterocycles, i.e., 1-3, will be presented and discussed. A simple and potentially general method by which a ketone carbonyl group in cage ketones can be replaced by an ether oxygen atom without concomitant rearrangement of the carbocyclic ring skeleton will be described. A key step in this approach involves MCPBA promoted oxidation of cage ketals to the corresponding cage-annulated carbonate ester. This approach has been applied to the synthesis of 3.



510.

IMPROVED SYNTHETIC PROCEDURES FOR 4,7,2',7'-TETRACHLORO AND 4',5'-DICHLORO-2',7'-DIMETHOXY 5(AND 6)-CARBOXYFLUORESCEINS. *Tim G. Carter, Matthew H. Lyttle, and Ronald M. Cook. Chemistry, Biosearch Technologies, Inc., 81 Digital Drive, Novato, CA 94949, fax: 415-883-8488, matt@solidphase.com*

Literature syntheses of 2',7'-dichloro-5(and 6)-carboxy-4,7-dichlorofluorescein ("5 and 6 TET") 1 and 4',5'-dichloro-2',7'-dimethoxy-5(and 6)-carboxyfluorescein ("5 and 6 JOE") 2 are reviewed, and new, prepatitively useful methods are presented. A three step synthesis of 1 was developed, which proved to be more efficient than the published seven step synthesis of this compound. The published synthesis of 2 proved difficult to reproduce, and a better workup of the key intermediate 2-chloro-4-methoxy resorcenol was devised. Purification of the dyes by open column chromatography is described.

511.

RAPID SYNTHESIS OF THE BK CHANNEL OPENER CGS 7181 AND ITS ANALOGS. *Michel Belley, Pascal Dubé, Sarah Dolman, and John Scheigetz. Medicinal Chemistry, Merck Frosst Center for Therapeutic Research, P.O. Box 1005, Kirkland, QC H9R 4P8, Canada, fax: 514-428-4936, belley@merck.com*

Calcium activated potassium (BK) channel openers are implicated in the excitability and the maintenance of the ionic homeostasis of the cells. They might be useful target for the treatment of disorders associated with excessive neuronal discharge such as epilepsy, urinary incontinence and irritable bowel syndrome. CGS 7181 and three of its analogs were reported by S. Hu and coworkers (Drug Dev. Res., 1997, 10-21) to be very potent and effective potassium channel openers, but there is no synthesis of these powerful compounds reported in the literature. Two synthetic routes to these compounds, from either commercially available 3-amino-4-bromobenzotrifluoride or 3-nitro-4-chlorobenzotrifluoride, with overall yields of 30-40%, will be described. The best synthetic sequence is summarized below. The cyanoester intermediate 1 is cyclized to the indole 2 by catalytic hydrogenation and the indole is N-aminated to 3 with O-(diphenylphosphoryl)hydroxylamine. Reaction with 4-tolylisocyanate yields the urea CGS 7181.